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REVIEWS

The Antiplatelet Effects of Organic Nitrates and Related Nitroso Compounds In Vitro and In Vivo and Their Relevance to Cardiovascular Disorders

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Organic nitrates, cornerstones of antianginal therapy, are believed to exert their principal anti-ischemic benefit by relaxing vascular smooth muscle. Recent evidence suggests that these compounds and related nitro(so) vasodilators are also potent platelet inhibitors. In view of the well recognized role of thrombotic events mediated by platelets in acute coronary syndromes, the antiplatelet effect of nitrates may also be of mechanistic importance in the treatment of these disorders. This review details the biochemical mechanism by which nitro(so) compounds inhibit platelet function and summarizes the in vitro and in vivo evidence that supports their antithrombotic effects.

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In the past decade, significant strides have been made in our understanding of the pathogenesis of ischemic coronary syndromes. As a result, the pharmacotherapy of patients with coronary artery disease has undergone noticeable changes. Perhaps the most remarkable change has been the introduction of antiplatelet therapy into the pharmacopoeia of cardiovascular medicine. This development is the direct consequence of overwhelming evidence that platelets are protagonists in unstable angina (1–3), myocardial infarction (2,4,5), sudden death (2,4,6), vasospastic angina (7,8) and, perhaps, hypertensive disorders (9,10). It is therefore noteworthy that despite the evolution of our conceptual and therapeutic approach to patients with cardiovascular disease, nitrates have survived intensive scrutiny to remain as mainstays of therapy for acute coronary syndromes (3,11–13).

Recent reviews (11,14–17) as well as reputable current cardiovascular texts (18,19) attribute the mechanism of the antiischemic action of nitrates and nitroprusside to their relaxant effects on vascular smooth muscle. Controversy persists as to the relative importance of coronary artery and arteriole dilation versus peripheral vasodilation in alleviating myocardial ischemia (11,14,16); however, the antiplatelet effects of nitro-vasodilators receive no mention despite the substantial number of published reports that have accumulated in this regard since the first demonstration (20) of the platelet inhibitory actions of nitroglycerin in 1967. Consequently, the clinician is generally unaware of the antiplatelet properties of organic nitrates and nitroprusside, and these agents are rarely considered part of the antiplatelet repertoire of cardiologists or potential contributors to iatrogenic bleeding diatheses (21).

In this report, we review the antiplatelet properties of organic nitrates and nitroprusside in vitro and in vivo. These data suggest that the antiplatelet effects of nitro compounds are of clinical relevance and therefore likely contribute to their beneficial mechanism of action in the acute ischemic syndromes of unstable angina and acute myocardial infarction.

Antiplatelet Effects of Organic Nitrates In Vitro

Early studies (20,22,23) uniformly demonstrated that nitroglycerin inhibited platelet aggregation. One such study by Schafer et al. (23) also revealed a weak platelet-inhibitory effect of isosorbide dinitrate. By that time, several investigators (24–28) had already shown that nitroprusside directly inhibits platelet aggregation and promotes platelet disaggregation. Thus, by 1980, each of the oxides of nitrogen commonly used in clinical practice had been demonstrated to exhibit antiplatelet properties in vitro. These findings notwithstanding, the concentrations of nitroglycerin and isosorbide dinitrate required to elicit inhibitory effects in vitro were not pharmacologically achievable in vivo and the

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biochemical mechanism by which nitrates act on platelets was poorly understood. The subsequent inability of Mehta and Mehta (29) to demonstrate platelet inhibition during intravenous nitroglycerin infusions further called into question the physiologic relevance of the in vitro findings. As we will discuss, however, each of these pertinent reservations about the relevance of the antiplatelet effects of organic nitrates and nitroprusside in vivo has now been addressed conclusively.

Mechanism of Action

Mellion et al. (30) first delineated the role of cyclic guanosine monophosphate (GMP) in the mechanism of platelet inhibition by nitrogen oxides. Extensive investigations by their group (31,32) and others (33,34) led to the discovery that nitric oxide and related nitroso compounds activate guanylate cyclase in a variety of tissues by a molecular mechanism involving the interaction of nitric oxide with the enzyme's heme group. Additionally, several investigators (31,35–37) recognized the reduced thiol requirement for maximal expression of guanylate cyclase activity and suggested that S-nitrosothiol adducts form as active intermediates in the metabolism of nitrates and related compounds. With this information in hand, Mellion et al. (30) demonstrated that nitric oxide and nitroprusside, which releases nitric oxide, inhibit platelet aggregation in association with marked increases in platelet cyclic GMP. These inhibitory responses were mimicked by the 8-bromo analogue of cyclic GMP and were prevented by methemoglobin, a hemoprotein with an affinity for nitric oxide. In later work, the same group (38) convincingly demonstrated the inhibitory potency of various synthetic S-nitrosothiols on human platelet aggregation and their activation of platelet guanylate cyclase in a heme-dependent manner.

Role of reduced thiols. Loscalzo (39) subsequently extended these observations to the study of organic nitrates, demonstrating that the reduced thiol N-acetylcysteine potentiated the platelet inhibitory actions of nitroglycerin by inducing the formation of S-nitroso-N-acetylcysteine. Importantly, by illustrating that the concentration of inhibitor reducing aggregation response by 50% (IC_{50}) for nitroglycerin is up to two orders of magnitude lower in the presence of N-acetylcysteine, the discrepancy between achievable in vivo concentrations of nitroglycerin and the higher concentrations required for in vitro inhibition could be adequately explained. Thus, provided that sufficient reduced thiol is available, pharmacologically achievable concentrations of nitroglycerin significantly inhibit platelet aggregation in vitro (39,40). Gerzer et al. (41) recently confirmed these observations by documenting a time-dependent liberation of nitric oxide from isosorbide dinitrate and nitroglycerin (as measured by guanylate cyclase activation and platelet inhibition) that is potentiated by cysteine.

The observation that denitrification and nitric oxide liberation from nitroglycerin are specifically dependent on the availability of the reduced thiol cysteine (35,37,42) suggests that factors that can lead to its depletion, such as the act of phlebotomy and other lengthy preparative techniques, may account in part for the variability in the antiplatelet response to organic nitrates. Cysteine is present in low micromolar concentrations in plasma and its means of replenishment through hepatic sulfur metabolism (43) are obviously compromised ex vivo. In contrast, because liberation of nitric oxide from nitroprusside is independent of cysteine (31), the provision of reduced thiol ex vivo is not required to unmask its antiplatelet effects. This theory is compatible with the greater in vitro potency of nitroprusside than that of organic nitrates. However, reduced thiols play a complex and multifactorial role in the metabolism of nitroso compounds and also potentiate the antiplatelet actions of nitroprusside (39). The biochemical mechanism by which nitro(so)-vasodilators inhibit platelet activation and, specifically, the role of reduced thiol in the inhibition mediated by nitroglycerin and nitroprusside are summarized in Figure 1.

Time dependence of nitric oxide elaboration from nitroglycerin. That nitric oxide liberation from nitroglycerin appears to be a time-dependent process (41) is also noteworthy. The usual evaluation of a drug's effect on platelet aggregation entails a brief preincubation period in platelet-rich plasma before aggregation is induced by the addition of an agonist. The demonstration that the platelet-inhibitory effects of nitroglycerin after 1 h of incubation exceed those at 2 min (41) provides an added explanation for the discrepancy between the relatively weak antiplatelet effects of nitroglycerin in previous in vitro studies in which preincubations have been of the order of minutes and its greater in vivo potency. Moreover, these data suggesting that nitric oxide generation from organic nitrates is slower than previously appreciated imply that the true in vitro antiplatelet profiles of nitroglycerin and isosorbide dinitrate have not been fully elucidated.

Cyclic GMP and platelet function. The biochemical and molecular mechanisms by which cyclic GMP modulates the intracellular events that follow receptor-mediated activation of platelets are an area of active investigation. The exposure of platelets to agonists of aggregation is associated with a burst in oxygen consumption, during which membrane arachidonate is converted to proaggregatory endoperoxides and thromboxane A_2 (44). Thromboxane synthesis enhances calcium mobilization, which in turn induces platelet secretion and promotes fibrinogen binding to the glycoprotein IIb/IIIa complex on the platelet surface (44–46). Surface receptor activation also results in phosphoinositide hydrolysis that facilitates calcium release from intracellular sites as well as platelet secretion (47). These inositol lipid-dependent functions are associated with phosphorylation of the platelet myosin light chain (20-kD protein) and a second 47-kD protein of unknown identity (47).

Nitroglycerin, isosorbide dinitrate and isosorbide-5-mononitrate attenuate the oxidation of arachidonate (23) and its conversion to thromboxane A_2 and hydroxy-5,8,10,-heptadecatrienoic acid (48) at concentrations that correlate

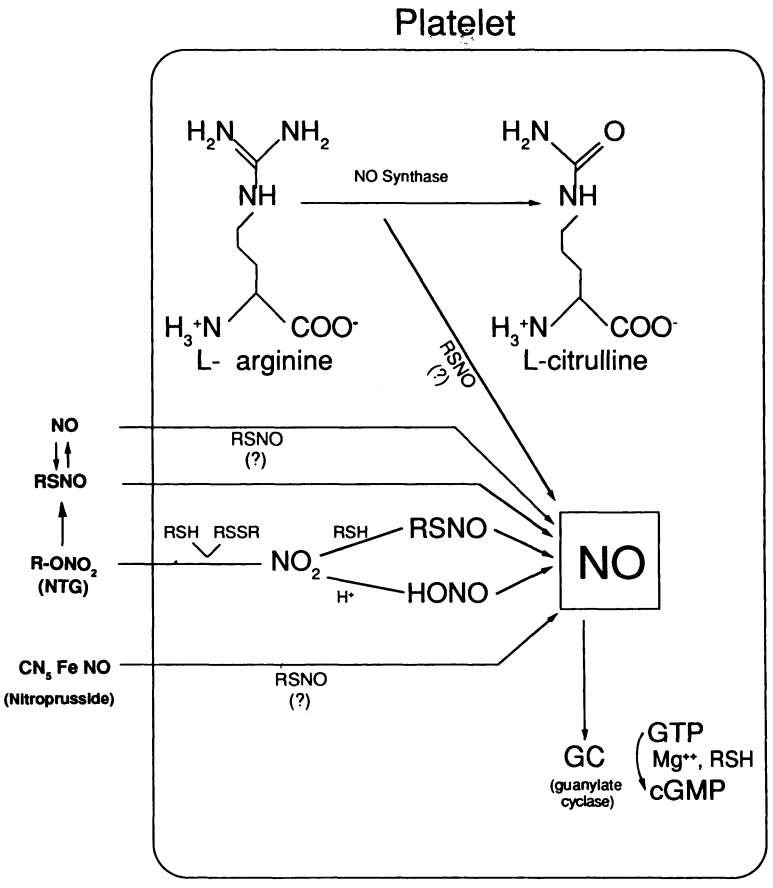

Figure 1. Schematic diagram of the proposed mechanism by which organic nitrates and related nitroso compounds inhibit platelet aggregation. Organic nitrates such as nitroglycerin (NTG) are metabolized to nitric oxide (NO), which complexes with the heme group of guanylate cyclase (GC) to activate the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). S-nitrosothiols (RSNO) are biologically active intermediates in this process, forming either extracellularly from protein-bound or low molecular weight reduced thiol (RSH) such as cysteine or intracellularly from the reduced thiol glutathione in a reaction catalyzed by glutathione-S-transferase. The generation of nitric oxide from nitroglycerin is also promoted by acidic conditions (H^+) that facilitate conversion of nitrite (NO_2) through nitrous acid (HONO) to nitric oxide. Nitroprusside spontaneously releases nitric oxide and the pathway by which it inhibits platelet activation is presumed to resemble closely that of an endothelium-derived relaxing factor with chemical properties of nitric oxide. However, the mechanism by which these nitroso species traverse the lipid membrane and deliver nitric oxide to the effector guanylate cyclase is not well understood. The platelet also contains an endogenous mechanism (nitric oxide synthase) for synthesis of nitric oxide from L-arginine, which may be involved in autoregulation of the aggregation response. CN_5FeNo = nitroprusside; RSSR = disulfide; $R\text{-}ONO_2$ = organic nitrate.

with their in vitro potencies as platelet inhibitors (20,22,23,41). Organic nitrates and nitroprusside also inhibit agonist-provoked increases in platelet cytosolic free calcium in a cyclic GMP-dependent manner (49), thus potentially explaining the attenuation of platelet secretion by organic nitrates such as teopranitol (50). However, unlike the analogous inhibition of cytosolic calcium increases in response to calcium channel blockers, the effects of nitro compounds are not dependent on external calcium concentration (23).

Accordingly, these observations suggest that cyclic GMP modulates intracellular platelet calcium availability by its interplay with phosphoinositide metabolism. Confirmatory evidence is provided by Deana et al. (51), who have recently shown that nitroprusside and the 8-bromo analogue of cyclic GMP inhibit agonist-dependent phosphorylation of the 20- and 47-kD proteins by interfering with the G-protein coupling of the surface receptor to phosphoinositide turnover. Mendelsohn et al. (personal communication) have preliminary data in support of this observation, revealing that nitrosothiols retard phosphoinositide hydrolysis. In addition, these investigators (52) have observed that the increases in cyclic GMP induced by S-nitroso-N-acetylcysteine correlate with inhibition of fibrinogen binding to the platelet surface glycoprotein IIb/IIIa receptor, thereby providing a molecular basis for the inhibitory actions of nitrogen oxides on the platelet aggregation response.

Effect on prostacyclin synthesis. Nitrates may inhibit platelets by indirect mechanisms that conceivably contribute to the alleged discrepancy between their in vivo and in vitro inhibitory potency. Interesting published studies addressing the effects of both organic nitrates and nitroprusside on endothelial prostaglandin metabolism support this contention. Levin et al. (53) first reported in 1981 that nitroglycerin induces human umbilical vein endothelial cells to synthesize prostacyclin. Shortly thereafter, they (54) reported that nitroprusside did not alter prostacyclin metabolism under similar conditions. In 1985, the same group (55) admitted they were unable to confirm their original observations for nitroglycerin and that isosorbide dinitrate was an equally ineffective agent in this regard. However, by the time of this recantation, two other groups (56,57) had confirmed their initial observations, further fueling the controversy.

Others (58,59) have since observed that the ability of nitrates to stimulate prostacyclin release is dependent on the presence of a free nitro group in an [exo] position, yet this mechanism does not fully explain the contradictory observations because this steric requirement is met by both nitroglycerin and isosorbide dinitrate. In reviewing 14 publications in favor of or against the nitroglycerin-prostacyclin hypothesis, Schror et al. (59) concluded that the use of different nitrate preparations may in part explain these discordant data. In keeping with this explanation, Gerzer et

al. (41) noted that batches of the same nitroglycerin formulation varied in their capacity to activate platelet guanylate cyclase by as much as one order of magnitude. We have also observed significant variability in the activity of different nitroglycerin preparations and among batches of the same formulation; however, the molecular explanation for this variation is not yet understood.

Synergistic inhibition of platelet function. The authors of several in vitro studies have argued that nitrogen oxides act synergistically with platelet-active prostaglandins to inhibit platelet aggregation. Levin et al. (54) suggested that nitroprusside interacts synergistically with prostacyclin to inhibit platelet function, MacDonald et al. (60) demonstrated "synergism" between nitric oxide and prostacyclin and De Caterina et al. (61,62) showed that isosorbide dinitrate and prostacyclin synergistically inhibit platelet aggregation. Although each of these studies fails to meet strict pharmacologic criteria for synergy (63), it is evident that prostacyclin enhances nitrate-mediated inhibition of platelet aggregation. We (64) recently demonstrated that nitroglycerin and prostaglandin E_2 interact synergistically to disaggregate platelets and that synergism occurs over a narrow range of pharmacologically achievable concentrations in vitro. However, it remains to be established whether pharmacologically achieved concentrations of organic nitrates or nitroprusside interact synergistically with antiplatelet endothelial products in vivo.

Antiplatelet action of metabolites of organic nitrates. De Caterina et al. (65) have raised the possibility that the antiplatelet properties of organic nitrates in vivo are a reflection of their metabolism to more active species. They demonstrated (62,65) that isosorbide-2-mononitrate inhibits platelet aggregation more effectively than does either isosorbide dinitrate or isosorbide-5-mononitrate. Moreover, because both hepatic mononitrate metabolites are longer lived in vivo than is the dinitrate, they (62,65) propose that metabolite generation may account for differences in antiplatelet potency in vivo and in vitro. The same may be true for nitroglycerin. It is well recognized that plasma levels of nitroglycerin correspond poorly with hemodynamic effects, an observation attributed to its complex hepatic and vascular smooth muscle metabolism (66,67). To our knowledge, the antiplatelet effects of the various nitroglycerin metabolites have not yet been examined in vitro to test this hypothesis.

Antiplatelet Effects of Organic Nitrates In Vivo and Ex Vivo

Nitroprusside. In 1979, Mehta and Mehta (28) studied 11 patients with congestive heart failure and 10 volunteers and convincingly demonstrated an antiplatelet effect for intravenous nitroprusside infusions titrated to one of several hemodynamic end points. This was evidenced by a decline in circulating platelet aggregates as well as ex vivo platelet aggregation responses to adenosine diphosphate (ADP) and epinephrine. More recently, these findings were verified by Hynes and Barash (68) in 29 patients undergoing coronary artery bypass surgery. Infusions of nitroprusside for blood pressure control during anesthesia resulted in dose-related decreases in platelet aggregation to ADP and epinephrine and were accompanied by prolonged bleeding times. In agreement with the in vitro evidence for the guanylate cyclase-dependent mechanism of platelet inhibition by nitro compounds, Hogan et al. (69) demonstrated elevations in intracellular platelet cyclic GMP in association with platelet inhibition by infusion of nitroprusside.

Isosorbide dinitrate and mononitrates. The data for isosorbide dinitrate are equally impressive. De Caterina et al. (70) infused this agent into 11 volunteers with angina at 4 mg/h for 30 min and demonstrated marked inhibition of ex vivo platelet aggregation and a decrement in circulating platelet aggregates. The nadir of the antiplatelet effect was delayed by 60 min from the time the infusion was terminated (that is, t = 90). Infusion at 30 mg/h for 20 min was often accompanied by a lesser antiplatelet effect attributed to excessive vasodilation that presumably evoked a compensatory sympathetic (proaggregatory) response (70). In a more recent study (65), the same investigators examined the effects of isosorbide-2-mononitrate and isosorbide-5-mononitrate infused at 4, 8 and 16 mg/h. Maximal ex vivo inhibition of platelet aggregation and thromboxane B_2 production were observed by 30 min after initiation of infusions and correlated in degree with hemodynamic changes (65). In contrast to the greater in vitro potency of isosorbide-2-mononitrate, these two mononitrate species exhibited very similar in vivo profiles when infused intravenously (66). The effects of orally administered isosorbide were evaluated in one study (71) in which 20 mg of isosorbide-5-mononitrate did not inhibit platelet aggregation; however, hemodynamic effects were not documented.

Reasons for lack of response to organic nitrates. In summary, data exist to support the view that nitroprusside and isosorbide dinitrate inhibit platelets in vivo. Their antiplatelet effects seem to correspond with hemodynamic changes, as long as the latter are not excessive. The antiplatelet effects of isosorbide dinitrate are delayed, presumably as a function of the time to achievement of peak plasma levels, the time required for their conversion to active metabolites and metabolic delays in denitrification and reduction to nitric oxide (41). A few patients appear to be relatively insensitive to organic nitrates. In light of the critical reliance on cysteine for denitrification, a deficiency of this thiol may contribute to a lack of nitrate responsiveness. Thus, the characteristic impairment of cysteine synthesis in hyperhomocysteinemic states (72,73) and the alterations in cysteine metabolism that may occur in hypertensive disorders (74) add yet another interesting twist to the concept of the "nitrate nonresponder."

Nitroglycerin. Available evidence also strongly supports an in vivo antiplatelet effect of nitroglycerin. Although these

data are more controversial, methodologic flaws readily account for the negative study results. Mehta and Mehta (29) reported that nitroglycerin infused intravenously at 55 ± 7 μg/min for a mean of 15 min, producing a decrease of 10 and 5 mm Hg in capillary wedge and mean arterial pressure, respectively, did not significantly inhibit platelet aggregation or reduce circulating platelet aggregates in seven patients with congestive heart failure. To date, their study represents the major testimony against an in vivo antiplatelet effect of nitroglycerin. However, there are several potential reasons for this negative result. First, the preceding studies of isosorbide dinitrate suggest that the antiplatelet effects of organic nitrates are related to hemodynamic responsiveness and are dependent on the duration of nitrate therapy (65,70). In the study of Mehta and Mehta (29), the hemodynamic effects were modest, with no significant alterations in blood pressure or systemic vascular resistance, and the duration of the infusion was suboptimal.

Low dose (5 μg/kg per min) nitroglycerin infusions in a canine model of coronary stenosis (75) likewise had negative results, as evidenced by the lack of change in cyclic platelet thrombus formation. In further examining the relation between the hemodynamic and platelet responses to nitroglycerin in this canine model, we confirmed (76) that a 5-μg/kg per min nitroglycerin infusion has little effect on either hemodynamic response or platelet aggregate formation. However, a 10-μg/kg per min infusion evoking a detectable (but modest) decrease in blood pressure was associated with obliteration of cyclic flow variation (76). Moreover, in keeping with the observations for isosorbide dinitrate, time dependence was demonstrated for the antiplatelet effects of nitroglycerin, which occurred maximally at approximately 30 min (76). In five healthy volunteers receiving high dose nitroglycerin infusions, Fitzgerald et al. (77) noted that the subject exhibiting the greatest hemodynamic sensitivity to nitroglycerin also demonstrated marked inhibition of ex vivo platelet aggregation. In that study, the assessment of platelet function was performed after 1 h of continuous nitroglycerin therapy.

Depletion of thiols during preparation of platelet-rich plasma ex vivo represents a second potential reason for the lack of observed platelet inhibition in the study of Mehta and Mehta (29). To assess this possibility in patients receiving nitroglycerin infusions titrated to a target systolic blood pressure, we repleted thiol stores with N-acetylcysteine ex vivo after preparing samples for platelet aggregation using standard techniques (40). In the absence of N-acetylcysteine repletion, intravenous nitroglycerin exhibited little effect on platelet function; however, aggregation was significantly inhibited by the addition of N-acetylcysteine at concentrations that alone did not affect platelet aggregation. These supportive data notwithstanding, measurements of platelet and plasma thiols during preparatory techniques have not been made, and further studies are required to elucidate the relation between platelet and plasma thiol availability at rest and the subsequent capacity of added reduced thiol to potentiate nitrate-mediated platelet inhibition.

In this context, it is noteworthy that thiol repletion with N-acetylcysteine may act by one of several mechanisms to potentiate the effects of nitroglycerin, including enhanced conversion of nitroglycerin to nitric oxide (42); generation of the antiplatelet compound S-nitroso-N-acetylcysteine (39); prolongation of the half-life of nitric oxide derived from nitroglycerin by formation of S-nitroso-N-acetylcysteine or by scavenging inhibitory oxygen-centered free radicals (78); and reduction of critical thiol groups in guanylate cyclase itself, including dithiols at the active site and possibly an activator site thiol (79–81).

The inability of Hogan et al. (82) to substantiate our findings in subjects receiving transdermal nitroglycerin (20 mg/24 h for 4 days) together with N-acetylcysteine (200 mg three times daily) is not surprising. This nitroglycerin regimen has been determined to induce tolerance and therefore the investigators' failure to assess hemodynamic responsiveness as an indication of treatment efficacy is a major study weakness. Moreover, the dose of N-acetylcysteine is well below the established level of 100 to 200 mg/kg that is required to potentiate the hemodynamic (83,84) and antiplatelet (76) actions of nitroglycerin in vivo. The contention that thiol depletion occurs ex vivo is further corroborated by the observations of Diodati et al. (85), who showed that platelet aggregation is attenuated in patients receiving intravenous nitroglycerin if it is measured in whole blood within 30 s of phlebotomy, whereas waiting 30 min results in loss of this effect.

Role of prostacyclin in platelet inhibition by nitroglycerin. The results of Diodati et al. (85) are equally supportive of an alternative explanation for the discrepancy between the in vivo and in vitro antiplatelet potency of organic nitrates. Because the half-life of prostacyclin is only 2 to 3 min (3,86), the loss of the ex vivo effects of nitroglycerin at 30 min in that study might be explained by the metabolism of prostacyclin ex vivo. In further support of this notion, Davis et al. (71) observed that the ex vivo IC_{50} for prostacyclin in platelet aggregation studies is shifted leftward in patients receiving oral isosorbide-5-mononitrate. In addition, two studies have demonstrated that nitroglycerin given either sublingually (87) or intravenously (88) prolongs bleeding time. In the study by Ring et al. (87), aspirin-induced prolongation of bleeding time was potentiated by nitroglycerin at 48 h but not at 2.5 to 3 h, therein corresponding with the time-dependent effects of aspirin on vascular endothelial cell cyclooxygenase. Thus, these data collectively implicate a role for prostacyclin in platelet inhibition by nitroglycerin in human subjects. Although the data do not differentiate between nitroglycerin-prostacyclin synergism and the possibility of nitroglycerin-induced prostacyclin generation, other (albeit contradictory) in vivo studies (77,89–91) do not strongly support the latter mechanism. Thus, in effect, the data favor a synergistic action between nitroglycerin and prostacyclin that may contribute

to the greater in vivo than in vitro potency of organic nitrates.

Relation of Organic Nitrate Metabolism and Action to Endothelium-Derived Relaxing Factor

It is likely that the antiplatelet effects of organic nitrate derivatives reviewed here have a physiologic counterpart. Endothelium-derived relaxing factor (EDRF) (92), one form of which is nitric oxide or a nitroso compound, has been shown to inhibit platelet aggregation and adhesion ex vivo (93). Furthermore, we have shown that this effect is potentiated by the reduced thiol N-acetylcysteine (94) in association with an increase in intracellular platelet cyclic GMP levels, again substantiating the potential role of thiols and the cyclic GMP signal cascade in the biologic action of oxides of nitrogen (Fig. 1).

Conclusions

Platelet activation is a harbinger of morbidity and mortality in several acute coronary ischemic syndromes (1–6,8). The use of aspirin in primary and secondary prevention trials (95–97) has been associated with a significant reduction in cardiovascular risk. However, it has not eliminated platelet-related morbidity, a finding that is in keeping with the in vitro observations (98–100) that aspirin possesses limited antiplatelet properties.

Therapeutic trends in the setting of acute myocardial infarction reveal nitrate therapy to be the most frequent intervention and its use has increased dramatically over time (101). A recent meta-analysis (102) showed that the use of intravenous nitroglycerin and nitroprusside in patients with acute myocardial infarction is typically associated with a 35% reduction in mortality, a degree of reduction that is unmatched by any of the existing accepted forms of therapy for acute myocardial infarction, including beta-adrenergic blockers and thrombolytic agents. Despite a general lack of objective evidence, recent recommendations (17,19) for nitrate therapy attest to the strong belief that these drugs are also beneficial in other ischemic syndromes in which platelets play a central role. The evidence for the antiplatelet effects of organic nitrates and nitroprusside has been conclusively demonstrated. These drugs potently disarm platelets of their ability to undergo primary and secondary wave aggregation (22,30,38,39), disperse already formed platelet clumps (30,64) and prevent platelet adhesion to damaged intimal linings (103,104).

Accordingly, inhibition of platelet function is an important property of organic nitrates and nitroprusside that more than likely contributes to their therapeutic efficacy in acute coronary syndromes. Thus, we advocate the use of nitrates as first-line agents in unstable angina and acute myocardial infarction. Prospective studies are needed to determine dosing regimens that most efficaciously inhibit platelet function, as well as patient subsets that are most likely to benefit from the use of these agents for their antiplatelet properties. Nitrates should also be given consideration in future trials for primary prevention of vascular diseases in which platelets have a proved role.

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